PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Patient-reported outcome measures in an outpatient parenteral antimicrobial therapy program– a prospective cohort study

Authors

Burch, Andrea Rahel; Ledergerber, Bruno; Ringer, Martin; Zinkernagel, Annelies S.; Eberhard, Nadia; Kaelin, Marisa B.; Hasse, Barbara

---

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Adekunle, Olajide A**
Affiliation	**Chapman University School of Pharmacy**
Date	**25-Feb-2024**
COI	**None**

Thank you for submitting this manuscript for review.

Abstract

Line 18: 7-14 days post-dis….. change to post-discharge.

Introduction

Line 59: It is recognized…. Put the citation.

Line 60: Individuals with chronic…. Put the citation to this statement

I think you should revise this introduction to reflect the justification and significance to the healthcare system.

Also, your objective seems to be too broad, “With this study, we aimed to assess….. I would advise you to state specifically, the objectives of the study. By doing so, you would prepare the readers’ minds and improves comprehension.

Methods

Line 109: change to “,” to “.”

Line 109: Start a new sentence with “The first interview…..”

Line 110: I guess the outpatient interview is the second interview? If so, indicate it in the description of the second interview as you did in line 109

Lines 122 – 123: Continuous variables were….. Categorical variables were….

Line 131: Delete "study results will be disseminated to the ……."

Results

Line 168: Swiss population averages were….. I noticed you did not mention swiss population average comparison in your method. Please, kindly add in the method section.

Table 2: You could add mean (95% CI) under inpatient, outpatient, and swiss population.

Line 177-178: Delete "Figure 2. Box…….." since you have it under the figure .

Discussion

Line 193: Change HrQoL to HRQoL

Line 205: Add "comma sign" after "During OPAT"

Lines 211 and 215: Find a way to add the authors' name in the manuscript, but not in form of APA citation. You could say ….from the study by Goodfellow and colleagues (14). Do the same for "Wee et al…

Line 227: Saillen et al., 2017

Line 229: Quintens et al, 2017

Line 237: non-complex

Line 240: HRQoL, not HRQo

Line 241: Lastly…

Conclusion

Your conclusion was only based on patients' experience and satisfaction with the OPAT team. However, you missed out on some facts on the HRQoL assessment which I think it's the major focus of the study. Kindly revise this part.

Referencing style

BMJ open journal uses Vancouver referencing style. Kindly change the style in your manuscript. Also, avoid combination of APA and Vancouver styles.

https://authors.bmj.com/writing-and-formatting/formatting-your-paper/

References

Please revise this section to reflect the accepted style. I recommend you use any of the referencing software or application, e.g Endnote, Mendeley, Zotero. It makes referencing easier.

Overall, I think you should spend some time to review literature on the topic. I know your study is relatively new, but you could get some articles to revise the introduction section and help comparing most of your findings in your study.

Reviewer **2**

Name **Rieg, Siegbert**

Affiliation **Universitatsklinikum Freiburg, Division of Infectious Diseases**

Date **25-Feb-2024**

COI **None**

Thank you for the opportunity to review the manuscript by Burch and colleagues.

The authors report on their experience with a monocentre OPAT program in Zurich. In this uncontrolled prospective cohort study the authors aim to investigate the impact of OPAT on the Health-related Quality-of-Life (HRQoL) using a shortened SF-36 questionnaire with 4 specific domains as primary outcome measures. Overall 33 patients were included. The follow-up visit was 7-14 days after discharge.

The manuscript contains new information on patient-reported outcomes in a difficult-to-treat patient subgroup suffering from complex infections. I have no major points concerning the general design of the study, however, there are some minor points (particularly concerning reporting, discussion of limitations inherent to the chosen design [uncontrolled cohort study] and cautious drawing of conclusions) the authors may consider to put their findings in context.

* Main outcome measures – could be referred to as co-primary outcomes

* Throughout the manuscript and particularly in conclusions in the abstract and in discussion line 195: Given the lack of a control group [which could have been OPAT 'candidates' in which initiation of outpatient management was planned but could not be realized] the conclusions of 'OPAT significantly impacts HRQoL' seems not justified. With any degree of convalescence, QoL may improve and this could be the natural course of "feeling better", i.e. also occurring with inpatient care. Although it may be plausible that OPAT has contributed to better scores, this was not shown in a controlled design – please rephrase the according sections throughout the manuscript and include this in limitations.

* 20/53 participants were excluded/were drop-outs as the second interview could not be performed: this may lead to relevant selection bias and should therefore be mentioned in limitations. To give some reassurance, the authors may consider to include results of the first interview in the supplement and compare the 33 included patients with the 20 'drop-outs'

Minor points

* Abstract line 18: should be ‘post-discharge’

* Abstract line 22: ‘role emotional’ please rephrase and explain briefly

* Introdution lines 46-61 – please give references for the outlined points

* Introduction line 47: I suggest to include ‘principles’ after antimicrobial stewardship

* Methods: The manuscript might benefit from outlining some definintions (e.g. cOPAT)

* Discussion line 205: unclear, what is meant – please rephrase

* Discussion line 230: Selection bias can never be ruled out completely... Suggest to modify along the lines: we aimed to rule out/minimize etc.

* Table 1: foreign body associated infections – please specify

---

Reviewer **3**

Name **Borchmann, Olivia**

Affiliation **Copenhagen University Hospital, Infectious Diseases, Hvidovre Hospital**

Date **27-Feb-2024**

COI **I have received financial support from GSK to participatein an HIV conference**

Thank you very much for presenting the manuscript Patient-reported outcome measures in an outpatient parenteral antimicrobial therapy program – a prospective cohort study

I think the manuscript presents some very interesting data. I have some questions particularly about the interpretation of results and the design, which I think the manuscript would benefit from including reflections about.

Suggested revisions:

Introduction:

1. Please add references to your introduction, particularly about the benefits of OPAT and about HRQoL (p. 3-4 ll 43-62).

2. There are some repetitions in the section about OPAT (p. 3 ll 48-56). Perhaps it could be shortened.

3. Could you please add a section to the introduction explaining what a PROM is, since you use that term in the title?

Methods

4. Perhaps it would be relevant to include some criteria or characteristics for the patients available for OPAT? How was the selection done? (p. 5 ll 65-71)

5. Was the shortened form of the SF-36 validated? Did you do the translation into German, or was there already a validated translated version of the SF-36? (p. 6. 101-108)

6. Do you think the modified timeframe of the SF-36 might influence the usefulness of the answers?

7. Did the interviews follow the SF-36 completely to ensure no interpretation was happening? To ensure that it remained a PROM? (p. 6 ll 109-114)

8. It is unclear whether you also use chi-square test and Fisher's exact test for the paired data or only to compare the ZOPAT and ZOPATlife. Can you please clarify in which part of your analyses you use which tests? (p. 7. ll 122-128)

Results/discussion

9. It seems very convincing that receiving OPAT compared to remaining in-patient would improve quality of life. However, I would like to hear your reflections in the manuscript about, whether that is what you are measuring. As I understand your design, you are comparing patients' HRQoL shortly before and shortly after discharge looking back 7 days. Perhaps adding a control population in a randomized design (where patients were randomized to either OPAT or remaining in-patient) was not possible. But how can you know that it is not only time passing from being admitted seriously ill and then getting so much better that discharge can be considered, that influences improvement in HRQoL? Your conclusions about the beneficial impact of OPAT on HRQoL are very strongly worded. Perhaps you can add some reflections and limitations to the discussion.

10. It is a great strength that you can compare baseline characteristics between participants in ZOPATlife and the rest of ZOPAT including dropouts. However, can you be sure that you eliminate selection bias through these comparisons? You have quite a large number of drop-outs who were not available for the second interview. Could those be the people who did not get better/were the most sick and could be thought not to have improved HRQoL? (p. 7 ll 136-143)

11. Could you please reflect about, whether there could be a bias in how positively participants evaluate OPAT in a non-anonymous interview with the OPAT research team? (p. 10 ll. 182-190, p. 11 ll. 219-229)

Conclusion

12. Where does the first part of your conclusion come from? (p. 13 ll 250-253)

Reviewer	**4**
Name	**Howell, Martin**

30.06.2024

Affiliation **The Children's Hospital at Westmead, Centre for Kidney Research**

Date **04-Mar-2024**

COI **None to declare**

Whilst the aim and objectives of the study are clear and in my opinion of relevance and importance to patients, unfortunately I do not consider that the study is able to answer the research question. I provide the following comments that I trust support my position.

1. The study is a small (only 33 completed the survey as required) single centre prospective cohort for which there is no control. The improvements noted at 7 to 14 days post discharge might be expected/have occurred irrespective of how the antimicrobial therapy is provided to patients. As there is no comparator there is no way of telling whether the OPAT program is associated with improvement in HRQoL that is greater than would have occurred with standard treatment. In short, the study design does not allow this to be determined and it is incorrect to say that the study “demonstrated how our local OPAT program affected HRQoL.”

2. The authors used a modified SF36. No justification is provided for the modification.

3. There is essentially no patient or public involvement even though this is a patient centred intervention.

4. The baseline SF36 scores seem only to be reported for those who completed the survey as in and out patients. Table 2 does not provide N, so it is possible that the inpatient score includes more than the 33 who completed the modified SF36 and both timepoints.

5. The abstract only provides P values and not the actual difference which is the critical data.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Olajide A Adekunle, Chapman University School of Pharmacy
Comments to the Author:
Thank you for submitting this manuscript for review.

Abstract

1. Reviewer 1: Line 18: 7-14 days post-dis….. change to post-discharge.

Answer. We thank the reviewer for the suggestion. We have adjusted the wording. (lines 19)

<u>**Introduction**</u>

2. Reviewer 1: Line 59: It is recognized…. Put the citation.

Answer: According to the suggestion of the reviewer we now reference the following paper as reference 11:

Powers JH, 3rd, Howard K, Saretsky T, Clifford S, Hoffmann S, Llorens L, Talbot G. Patient-Reported Outcome Assessments as Endpoints in Studies in Infectious Diseases. Clin Infect Dis. 2016;63 Suppl 2(Suppl 2):S52-6. doi:10.1093/cid/ciw317

3. Reviewer 1: Line 60: Individuals with chronic…. Put the citation to this statement

Answer: Thank you for your suggestion. We have deleted this statement in order to shorten the text, and since the statement seems redundant with the previous sentence

4. Reviewer 1: I think you should revise this introduction to reflect the justification and significance to the healthcare system. Also, your objective seems to be too broad, "With this study, we aimed to assess….. I would advise you to state specifically, the objectives of the study. By doing so, you would prepare the readers' minds and improves comprehension

Answer. The reviewer is correct that our objective as too broad. We revised the abstract (lines 13-15) and the introduction section accordingly (lines 68-69):

Abstract: *"To evaluate the improvements in the mean SF-36 score [95% CI] from pre-discharge to post-discharge among prospective participants of a Swiss Outpatient Parenteral Antimicrobial Therapy (OPAT) program using Patient Reported Outcomes (PROs)."*

Introduction: *"With this study, we aimed to assess the improvements in the mean SF-36 score (95% CI) from interview 1 to 2 among prospective participants of a Swiss Outpatient Parenteral Antimicrobial Therapy (OPAT) program."*

Methods

5. Reviewer 1: Line 109: change to "," to "."

Answer: This correction has been done (line 121).

6. Reviewer 1: Line 109: Start a new sentence with "The first interview….."

Answer: Done (line 121).

7. Reviewer 1: Line 110: I guess the outpatient interview is the second interview? If so, indicate it in the description of the second interview as you did in line 109

Answer. This correction has been done (lines 121-123). It now reads:

"*The first interview took place shortly before discharge (as an inpatient) and the second interview took place 7 to 14 days after discharge (as an outpatient).*"

8. Reviewer 1: Lines 122 – 123: Continuous variables were….. Categorical variables were….

Answer: The sentence is now in past tense as suggested (lines 137-138):

"Continuous variables were expressed as medians and interquartile ranges (IQRs). Categorical variables were presented as numbers and percentages."

9. Reviewer 1: Line 131: Delete "study results will be disseminated to the ……."

Answer. The sentence has been deleted from the patient and public involvement section (lines 145-146).

Results

10. Reviewer 1: Line 168: Swiss population averages were….. I noticed you did not mention Swiss population average comparison in your method. Please, kindly add in the method section.

Answer. We added the following sentence in the method section (lines 134-135): *"The SF-36 scores reached by the ZOPATlife patients were also compared with the SF-36 scores observed in the Swiss population[20]"* Please refer to reference 20 of the revised manuscript.

11. Reviewer 1: Table 2: You could add mean (95% CI) under inpatient, outpatient, and Swiss population.

Answer. Thank you for this suggestion, we have added this information in **Table 2**.

12. Reviewer 1: Line 177-178: Delete "Figure 2. Box…….." since you have it under the figure .

Answer: Thank you for pointing this out. Since we need to specify where Figure 2 should be inserted, we must keep this label in its current position. To enhance clarity, we have added an extra line to make the label's purpose more visually evident (lines 200-202).

Discussion

13. Reviewer 1: Line 193: Change HrQoL to HRQoL

Answer: We corrected this inconsistency throughout the discussion.

14. Reviewer 1: Line 205: Add "comma sign" after "During OPAT"

Answer: The whole sentences was revised (line 229-232).

15. Reviewer 1: Lines 211 and 215: Find a way to add the authors' name in the manuscript, but not in form of APA citation. You could say ….from the study by Goodfellow and colleagues (14). Do the same for "Wee et al…

Answer: We have rephrased the sentences as suggested by the reviewer:

*"This finding aligns with findings from the study of Goodfellow and colleagues,[26] which indicated that the component summaries reflecting physical strength did not significantly change during OPA*T."

(lines 236-238)

and

"This may explain why we cannot estimate the percentage of patients returning to work after discharge, as was done by Wee and colleagues.[27]"(lines 240-241)

16. Reviewer 1: Line 227: Saillen et al., 2017

Answer. We have rephrased the sentences as suggested by the reviewer:

"This aligns with findings from Saillen and colleagues,[28] where 97% of patients expressed a preference for this type of care, and would have recommended the local OPAT program to others."

(line 253-254)

17. Reviewer 1: Line 229: Quintens et al, 2017

Answer. We have rephrased the sentences as suggested by the reviewer:

"This finding is also consistent with the results of Quintens and colleagues.[8,2]" (line 255)

18. Reviewer 1: Line 237: non-complex

Answer. We changed "noncomplex" to "non-complex" as suggested by the reviewer. (line 263-264)

19. Reviewer 1: Line 240: HRQoL, not HRQo

Answer: Done. Please refer also to point 13, Reviewer 1.

20. Reviewer 1: Line 241: Lastly…

Answer: We changed "last" to "lastly" as suggested by the reviewer. (line 281)

Conclusion

21. Reviewer 1: Your conclusion was only based on patients' experience and satisfaction with the OPAT team. However, you missed out on some facts on the HRQoL assessment which I think it's the major focus of the study. Kindly revise this part.

Thank you for this statement. We added the findings regarding HRQoL and put it into context. It now reads:

"Patients experienced significant improvements in HRQoL from just before discharge to the period in OPAT. It remains unclear whether this was due to the OPAT program itself or to the circumstances of improved health in general. Either way, the shift to outpatient care improves communication between healthcare providers and patients. Regular follow-up visits and close monitoring of patients in their home environment create a more personalized and attentive care expe-rience. This increased interaction and support helps patients better understand their treatment plan and fosters a sense of partnership, resulting in high patient satisfaction as showed in this study." (lines 291-296)

Referencing style

22. Reviewer 1: BMJ open journal uses Vancouver referencing style. Kindly change the style in your manuscript. Also, avoid combination of APA and Vancouver styles.

https://authors.bmj.com/writing-and-formatting/formatting-your-paper/

Answer: Thank you for this suggestion. We adapted all citations consequently to reference style Vancouver, in this case, this meant:

- in-text references: consist of consecutive numbers formatted in superscript and placed after the period.
- Bibliography: all the authors listed for the article were included

References

23. Reviewer 1: Please revise this section to reflect the accepted style. I recommend you use any of the referencing software or application, e.g Endnote, Mendeley, Zotero. It makes referencing easier.

Answer: We revised this section, thank you for this point. Please refer to point 22, Reviewer 1.

24. Reviewer 1: Overall, I think you should spend some time to review literature on the topic. I know your study is relatively new, but you could get some articles to revise the introduction section and help comparing most of your findings in your study.

Answer: We revised the introduction and added new references. (lines 44-69)

Reviewer: 2

Dr. Siegbert Rieg, Universitatsklinikum Freiburg

Comments to the Author:

Thank you for the opportunity to review the manuscript by Burch and colleagues.

The authors report on their experience with a monocentre OPAT program in Zurich. In this uncontrolled prospective cohort study the authors aim to investigate the impact of OPAT on the Health-related Quality-of-Life (HRQoL) using a shortened SF-36 questionnaire with 4 specific

domains as primary outcome measures. Overall 33 patients were included. The follow-up visit was 7-14 days after discharge.

The manuscript contains new information on patient-reported outcomes in a difficult-to-treat patient subgroup suffering from complex infections. I have no major points concerning the general design of the study, however, there are some minor points (particularly concerning reporting, discussion of limitations inherent to the chosen design [uncontrolled cohort study] and cautious drawing of conclusions) the authors may consider to put their findings in context

Answer: We thank the reviewer for his comments.

1. Reviewer 2: **Main outcome measures – could be referred to as co-primary outcomes**

Answer. According to the suggestion of the reviewer "main outcome measures" has been rephrased to "co-primary outcomes". (line 22)

2. Reviewer 2: Throughout the manuscript and particularly in conclusions in the abstract and in discussion line 195: Given the lack of a control group [which could have been OPAT 'candidates' in which initiation of outpatient management was planned but could not be realized] the conclusions of 'OPAT significantly impacts HRQoL' seems not justified. With any degree of convalescence, QoL may improve and this could be the natural course of "feeling better", i.e. also occurring with inpatient care. Although it may be plausible that OPAT has contributed to better scores, this was not shown in a controlled design – please rephrase the according sections throughout the manuscript and include this in limitations.

Answer: We agree with the reviewer: We rephrased the conclusion of the abstract as follows: *"Patients experienced significant improvements in HRQoL while enrolled in OPAT and the program yields high patient satisfaction. Hospitals considering new OPAT programs should include both patient satisfaction and HRQoL impact in their argument repertoire for the introduction of OPAT."* (lines 27-29)

We also rephrased the first paragraph of the discussion:

"The findings of this study demonstrated significant improvements in HRQoL for patients, as evidenced by comparing SF-36 scores shortly before discharge to those during OPAT." (lines 219-220)

Additionally we added the following section in the limitations section of the discussion:

"This study suggests that the better HRQoL scores achieved are likely due to outpatient treatment rather than general recovery from illness. As patients convalesce, their quality of life may naturally improve, which could occur with inpatient care as well. While it is plausible that OPAT has contributed to better scores, we could not demonstrate this in a con-trolled manner. Unfortunately, we could not establish a control group of potential OPAT candidates without outpatient therapy." (lines 265-269)

3. Reviewer 2: 20/53 participants were excluded/were drop-outs as the second interview could not be performed: this may lead to relevant selection bias and should therefore be mentioned in limitations. To give some reassurance, the authors may consider to include results of the first interview in the supplement and compare the 33 included patients with the 20 'drop-outs'

Answer: We agree with the reviewer and added Table S2 to the supplementary information to illustrate the patient characteristics and treatments from patients with one compared to patients with two interviews. We also present the different outcomes as mean scores (95% CI) for each domain among the first interview of patients who completed both versus one the first interview in table S3 (mentioned in the text line line 176).

We also mention this point in the limitations section of the discussion:

"We could not perform the second interview in 38% of patient which: may lead to relevant selection bias. However, when comparing patients with one or two interviews, we did not detect significant differences besides from the emotional role." (lines 273-275)

Minor points

4. Reviewer 2: * Abstract line 18: should be 'post-discharge'

Answer: Done (line 19).

5. Reviewer 2: Abstract line 22: 'role emotional' please rephrase and explain briefly

Answer: Thank you for this suggestion. The results section of the abstract now reads*:*

"Specifically, participants reported improvements in the mean SF-36 score [95% CI] from interview 1 to 2 for "emotional role" (24.2 [5.0-43.5]), "social functioning" (22.0 [95% CI 10.8-33.2]) and "emotional well-being" (11.9 [95%CI 5.6-18.2])." (lines 24-26).

6. Reviewer 3: Introduction lines 46-61 – please give references for the outlined points

Answer: We revised the introduction. Please find the references directly in the revised manuscript. The mentioned section now reads:

"OPAT also reflects a comprehensive approach to patient care aligning with antimicrobial stewardship [REF]. OPAT represents a paradigm shift in the delivery of antimicrobial therapy, allowing patients to receive necessary treatments from the comfort of their homes. This transition from in- to outpatient care is a key contributor to the positive experiences reported by patients undergoing OPAT [REF]. Several factors might contribute to the patient satisfaction associated with OPAT. Primarily the freedom it provides patients without the constraints of a hospital stay. Patients maintain their normal daily routine, minimizing disruptions to work, family life, and social engagement. Moreover, the close outpatient care provided by the professional OPAT team [REF] are factors influencing patient satisfaction with OPAT. By administering treatment in a home environment, the likelihood of exposure to hospital-acquired infections is reduced, possibly fostering a sense of safety and well-being among patients.

To determine which approach best meets the patient's needs, values and preferences, it is essential to incorporate the patient's perspective. Patient Reported Outcome (PRO) is a type of clinical outcome assessment (COA) where the report comes directly from the patient. Patients respond to questions about their health condition without any alteration or interpretation [REF]. Instruments used to measure and record PRO are known as Patient Reported Outcome Measures (PROMs). Some PROMs instruments aim to describe or measure health in general (or generic) manner, allowing the same

questions to be used for patients with diverse conditions. The concepts measured by these PROs should encompass broader aspects of Health-Related Quality of Life (HRQoL) [REF]*. HRQoL, according to CDC* [REF]*, refers to an individual's or group's perceived physical and mental health over time. HRQoL encompasses various dimensions, such as physical, mental, emotional, and social functioning* [REF]*. Serving as a patient-centered measure, HRQoL complements objective disease indicators and has the potential to predict morbidity and mortality* [REF]*. It is recognized that patients with infections may experience impaired health-related quality of life* [REF]*, and such impairments can endure even after the infection has resolved."* (line 48-68)

7. Reviewer 2: Introduction line 47: I suggest to include 'principles' after antimicrobial stewardship

Answer: Done as suggested. (line 49)

8. Reviewer 2: * Methods: The manuscript might benefit from outlining some definintions (e.g. cOPAT)

Answer: We agree with the reviewer and now explain the term cOPAT in the methods section.

"*Complex Outpatient Antibiotic Therapy (cOPAT) offers long-term oral antibiotic management with frequent monitoring and reviews. The cOPAT team, part of the Outpatient Parenteral Antibiotic Therapy (OPAT) service, provides intra-venous antibiotics for patients who do not need hospitalization."* (line 109-111).

9. Reviewer 2: Discussion line 205: unclear, what is meant – please rephrase

Answer: We rephrased/completed the sentence. It now reads*:*

"This finding suggests that the combination of disease recovery and home treatment has a significant impact on HRQoL. This seemed to be independent of the potentially higher workload from the individual's perspective during OPAT: patients have to actively organize medicines and supplies and home care together with the OPAT nurse, as well as managing daily activities such as cooking or personal care." (lines 227-232*)*

10. Reviewer 2: * Discussion line 230: Selection bias can never be ruled out completely. Suggest to modify along the lines: we aimed to rule out/minimize etc.

Answer: We modified the sentence. It now reads:

*"One strength of our study was, that we tried to minimize a possible selection bias by comparing the ZOPAT cohort to the ZOPATlife cohort." (*line 256-257)

We also highlight our limitations. (lines 260-284)

11. Reviewer 2: Table 1: foreign body associated infections – please specify

Answer: We added the following specification in the footnote of Table 1:

"[1] *prosthetic joint infections, vascular graft infections, breast implant infections*."

Reviewer 3

Miss Olivia Borchmann, Copenhagen University Hospital

Comments to the Author:

General

Thank you very much for presenting the manuscript Patient-reported outcome measures in an outpatient parenteral antimicrobial therapy program – a prospective cohort study I think the manuscript presents some very interesting data. I have some questions particularly about the interpretation of results and the design, which I think the manuscript would benefit from including reflections about.

Answer: We thank the reviewer for this statement.

Suggested revisions:

Introduction:

1. Reviewer 3. Please add references to your introduction, particularly about the benefits of OPAT and about HRQoL (p. 3-4 ll 43-62).

Answer. We thank the reviewer for these suggestions. We added Tamma and colleagues 2017; Burch and colleagues 2024; Powers and colleagues 2016; Alzaharani N and colleagues 2021; Megari K and colleagues 2013 to underline the evidence for the statements made in this section (please refer to lines 44-69).

2. Reviewer 3: There are some repetitions in the section about OPAT (p. 3 ll 48-56). Perhaps it could be shortened.

Answer: We thankfully accepted your suggestion and shortened the text. It now reads (without references):

"OPAT represents a paradigm shift in the delivery of antimicrobial therapy, allowing patients to receive necessary treatments from the comfort of their homes. This transition from in- to outpatient care is a key contributor to the positive experiences reported by patients undergoing OPAT. Several factors might contribute to the patient satisfaction associated with OPAT. Primarily the freedom it provides patients without the constraints of a hospital stay. Patients maintain their normal daily routine,

minimizing disruptions to work, family life, and social engagement. Moreover, the close outpatient care provided by the professional OPAT team are factors influencing patient satisfaction with OPAT. By administering treatment in a home environment, the likelihood of exposure to hospital-acquired infections is reduced, possibly fostering a sense of safety and well-being among patients." (line 49-56)

3. Reviewer 3: Could you please add a section to the introduction explaining what a PROM is, since you use that term in the title?

We added a section to introduce the term PROM:

"Instruments used to measure and record PRO are known as Patient Reported Outcome Measures (PROMs). Some PROMs instruments aim to describe or measure health in general (or generic) manner, allowing the same questions to be used for patients with diverse conditions." (lines 60-61)

Methods

4. Reviewer 3: Perhaps it would be relevant to include some criteria or characteristics for the patients available for OPAT? How was the selection done? (p. 5 ll 65-71)

Answer: We added the following sentence to clarify the patient referral process:

"Referrals to the OPAT team are made when it is clear during the inpatient stay that parenteral antibiotic therapy will extend beyond the required hospitalization period or when parenteral antibiotic therapy is needed for targeted treatment, but hospitalization is not necessary." (line 73-75)

5. Reviewer 3: Was the shortened form of the SF-36 validated? Did you do the translation into German, or was there already a validated translated version of the SF-36? (p. 6. 101-108)

Answer: The shortened form of the SF-36 did not change the structure of the form in the different domains and by this, did not change questions or analysis of the questionnaire. The adaption consisted in excluding nonessential domains for evaluating HRQoL changes due to the OPAT program. We added the following information for clarification*: "[…] without changing the structure of the questionnaire domains*." (line 116)

We used the validated German translation (Morfeld and colleagues 2011). We added this information in the manuscript*: "The validated German translation*[REF] *was used for the survey in German.*" (line 114-115)

6. Reviewer 3: Do you think the modified timeframe of the SF-36 might influence the usefulness of the answers?

Answer*:* Thank you for your question. We believe the modified timeframe does not affect the usefulness of the study. The questions in the used domains focused on feelings and well-being, which can vary daily and do not require a longer period to manifest (unlike physical fitness for example). Additionally, with OPAT having a median treatment duration of 10 days (see Burch et al, 2024) extending the timeframe was not feasible.

7. Reviewer 3: Did the interviews follow the SF-36 completely to ensure no interpretation was happening? To ensure that it remained a PROM? (p. 6 ll 109-114)

Answer: Yes, the interviews followed the SF-36 strictly. We added this information in the manuscript: "*A trained investigator conducted the interviews, strictly adhering to the SF-36 to ensure no misinterpretation."* (line 121)

8. Reviewer 3: It is unclear whether you also use chi-square test and Fisher's exact test for the paired data or only to compare the ZOPAT and ZOPATlife. Can you please clarify in which part of your analyses you use which tests? (p. 7. ll 122-128)

Answer: Thank you for this question. The reviewer is correct; we only used Fisher's exact test. We corrected the statistics part of the manuscript accordingly:

"The Fisher's exact test was used for comparing categorical variables, while the Wilcoxon rank-sum test was used for continuous variables." (lines 138-139)

Results/discussion

9. Reviewer 3: It seems very convincing that receiving OPAT compared to remaining in-patient would improve quality of life. However, I would like to hear your reflections in the manuscript about, whether that is what you are measuring. As I understand your design, you are

comparing patients' HRQoL shortly before and shortly after discharge looking back 7 days. Perhaps adding a control population in a randomized design (where patients were randomized to either OPAT or remaining in-patient) was not possible. But how can you know that it is not only time passing from being admitted seriously ill and then getting so much better that discharge can be considered, that influences improvement in HRQoL? Your conclusions about the beneficial impact of OPAT on HRQoL are very strongly worded. Perhaps you can add some reflections and limitations to the discussion.

Answer: We agree with the reviewer. Reviewer 2 raised the same concern, and we have made the necessary adjustments to the manuscript. For details, please refer to Point 2 in Reviewer 2's comments.

10. Reviewer 3: It is a great strength that you can compare baseline characteristics between participants in ZOPATlife and the rest of ZOPAT including dropouts. However, can you be sure that you eliminate selection bias through these comparisons? You have quite a large number of drop-outs who were not available for the second interview. Could those be the people who did not get better/were the most sick and could be thought not to have improved HRQoL? (p. 7 ll 136-143)

Answer: The reviewer is correct. Actually, readmission accounted for the dropout of 3 out of the 20 patients, but clinical deterioration was the cause of readmission in only one case. We have added Table S2 to the supplementary information to illustrate the characteristics and treatments of patients with one interview compared to those with two interviews. Additionally, we present the different outcomes as mean scores (95% CI) for each domain from the first interview of patients who completed both interviews versus those who completed only the first interview (Table S3). Please refer also to point 3, reviewer 2:

11. Reviewer 3: Could you please reflect about, whether there could be a bias in how positively participants evaluate OPAT in a non-anonymous interview with the OPAT research team? (P. 10 ll. 182-190, p. 11 ll. 219-229)

Answer: We added the following part in the discussion section: *"Regarding the patient's evaluation of the program, it should be noted that the interviews were not anonymous, which could influence the*

answers given by the patient. However, a trained person who was not directly involved in the patient's treatment conducted the interview in order to counteract this bias." (lines 279-281)

Conclusion

12. Reviewer 3: Where does the first part of your conclusion come from? (p. 13 ll 250-253)

Answer: The reviewer is right that this first part stands alone with no obvious derivation. We have adapted the section and it now reads:

*"Patients experienced significant improvements in HRQoL from just before discharge to the period in OPAT. It remains unclear whether this was due to the OPAT program itself or to the circumstances of improved health in general. Either way, the shift to outpatient care improves communication between healthcare providers and patients. Regular follow-up visits and close monitoring of patients in their home environment create a more personalized and attentive care experience. This increased interaction and support helps patients better understand their treatment plan and fosters a sense of partnership, resulting in high patient satisfaction, as shown in this study. As hospitals consider establishing or expanding OPAT programs, recognizing the impact on patient satisfaction is critical. Incorporating patient satisfaction metrics into the evaluation of OPAT programs can provide valuable insight into the success and effectiveness of these initiatives. Moreover, patient and public involvement should be used in the planning of a future study for assessing outcomes meaningful for the patients. By prioritizing patient-centred care and continuously improving the OPAT experience, healthcare organizations can improve not only clinical outcomes, but also the overall satisfaction and well-being of individuals undergoing outpatient antimicrobial therapy." (*line 291-302*)*

Reviewer: 4

Dr. Martin Howell, The Children's Hospital at Westmead, University of Sydney

Comments to the Author:

Whilst the aim and objectives of the study are clear and in my opinion of relevance and importance to patients, unfortunately I do not consider that the study is able to answer the research question. I provide the following comments that I trust support my position.

1. Reviewer 4: The study is a small (only 33 completed the survey as required) single centre prospective cohort for which there is no control. The improvements noted at 7 to 14 days post discharge might be expected/have occurred irrespective of how the antimicrobial therapy is provided to patients. As there is no comparator there is no way of telling whether the OPAT program is associated with improvement in HRQoL that is greater than would have occurred with standard treatment. In short, the study design does not allow this to be determined and it is incorrect to say that the study "demonstrated how our local OPAT program affected HRQoL."

Answer: The reviewer is correct and as also suggested by reviewer 2 (point 2) and reviewer 3 (point 9) we acknowledge this limitation. We also softened the tonality of our conclusion.

*"Patients experienced significant improvements in HRQoL from just before discharge to the period in OPAT. It remains unclear whether this was due to the OPAT program itself or to the circumstances of improved health in general." (*line 291-292*)*

2. Reviewer 4: The authors used a modified SF36. No justification is provided for the modification.

Answer: Median OPAT treatment duration in our program is 10 days. Hence, a more extended time-period for the second interview would not make any sense. Please also refer to point 6 or reviewer 3.

3. Reviewer 4: There is essentially no patient or public involvement even though this is a patient centred intervention.

Answer: The reviewer is correct. Patient and public involvement (PPI) is essential in the context of planning and conducting a scientific study and in assessing outcomes meaningful for the patient. We have indicated in the conclusions section that PPI should be evaluated in a future study:

"Moreover, patient and public involvement should be used in the planning of a future study for assessing outcomes meaningful for the patient." (Lines 299-301)

4. Reviewer 4: The baseline SF36 scores seem only to be reported for those who completed the survey as in and out patients. Table 2 does not provide N, so it is possible that the inpatient score includes more than the 33 who completed the modified SF36 and both timepoints.

Answer: Thank you for this valuable feedback. Actually, n is 33 for both groups but you are right, that this information is not included in the table. We completed the table in the revised version of Table 2.

5. Reviewer 4: The abstract only provides P values and not the actual difference which is the critical data.

Answer: Please refer also to point 5, reviewer 2.

"*Specifically, participants reported improvements in the mean SF-36 score [95% CI] from interview 1 to 2 for "emotional role" (24.2 [5.0-43.5]), "social functioning" (22.0 [95% CI 10.8-33.2]) and "emotional well-being" (11.9 [95%CI 5.6-18.2])."* (lines 23-26).

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Rieg, Siegbert**
Affiliation	**Universitatsklinikum Freiburg, Division of Infectious Diseases**
Date	**19-Jul-2024**

COI None to declare.

The authors have adequately addressed and answered all points and questions raised by the reviewers and editor.

Reviewer 3

Name Borchmann, Olivia

Affiliation Copenhagen University Hospital, Infectious Diseases, Hvidovre Hospital

Date 01-Aug-2024

COI I have received financial support from GSK to participatein an HIV conference.

Thank you for letting me review Manuscript ID bmjopen-2024-084727.R1, entitled "Patient-reported outcome measures in an outpatient parenteral antimicrobial therapy program– a prospective cohort study."

In general, I think the authors have taken the reviewers' comments into consideration and made revisions accordingly in a meaningful way. I think the manuscript could also benefit from a general language check.

I have a few following minor comments. Pages and line numbers refer to the version of the manuscript with the edits highlighted.

Strengths and limitations:

Pg 32, ll 17-19: I am still a bit hesitant about your wording about selection bias being unlikely. Doesn't your comparison with the entire OPAT group have more to do with the external validity (depending on how you define your study population and inclusion of course (see comment under methods)? I think, your risk of selection bias still has to do with the drop-outs, which still has quite a high number. I think it is great that you are able to compare the results of the first questionnaire between the drop-outs and the study participants, but that does not rule out selection bias as you have also acknowledged in your discussion.

Introduction:

Pg 33, l. 68: Please add citation.

Pg 33, ll. 81-82, please add again pre- and post-discharge after interview 1 and 2.

Methods:

Pg. 35-36, ll. 144-147: I am getting a bit confused about your date of inclusion/baseline date. In ll 144-146 you state that participants are included only after finishing the second

interview. But is the date of the second interview then your baseline date and the date of your baseline data collection? Why do you then consider those who did not respond to the second questionnaire as excluded/drop-outs? Please clarify in the manuscript and revise figure 1, results, and discussion accordingly.

Results:

Pg. 41, ll. 222-223: The sentence "The SF-36 scores for all domains were lower at baseline for inpatients than for outpatients 222 but never reached the levels observed in the Swiss population." is confusing. Please consider splitting it into two sentences so that it doesn't read like low SF-36 scores are better.

Discussion:

Pg 42, ll. 263-270: Some lines have been dublicated. Please delete.

Pg. 44, ll. 309: The sentence: "This study suggests that the better HRQoL scores achieved are likely due

to outpatient treatment rather than general recovery from illness." is confusing. I don't think your study in itself suggests that better HRQoL scores are due to OPAT, but that is rather a point you wish to argue in the discussion, which you do well. Please consider revising that sentence.

In general, I suggest you revise the order of the different sections in the discussion so that the sections about selection bias follow each other and the sections about the effect of OPAT vs. convalescence follow each other.

Conclusion:

Pg 46, l. 348: Please insert domains after HRQoL.

VERSION 2 - AUTHOR RESPONSE

Reviewer 3:

1. Pg 32, ll 17-19: I am still a bit hesitant about your wording about selection bias being unlikely. Doesn't your comparison with the entire OPAT group have more to do with the external validity (depending on how you define your study population and inclusion of course (see comment under methods)? I think, your risk of selection bias still has to do with the drop-outs, which still has quite a high number. I think it is great that you are able to compare the results of the first questionnaire between the drop-outs and the study participants, but that does not rule out

selection bias as you have also acknowledged in your discussion.

Answer: We thank for this comment. We adapted the statement. It now reads:

"By comparing the characteristics of patients of all OPAT patients (ZOPAT cohort) with the OPAT patients included in this study (ZOPATlife cohort) we were able to show, that the two groups did not differ significantly." (lines 37-38)

2. Pg 33, l. 68: Please add citation.

Answer: Done as suggested. (line 56)

3. Pg 33, ll. 81-82, please add again pre- and post-discharge after interview 1 and 2.

Answer: we thank the reviewer for his comment. We have added "pre-discharge" and "post-discharge" after the numbering of the interviews. (line 69)

4. Pg. 35-36, ll. 144-147: I am getting a bit confused about your date of inclusion/baseline date. In ll 144-146 you state that participants are included only after finishing the second interview. But is the date of the second interview then your baseline date and the date of your baseline data collection? Why do you then consider those who did not respond to the second questionnaire as excluded/drop-outs? Please clarify in the manuscript and revise figure 1, results, and discussion accordingly.

Answer: Patients qualifying for OPAT and who provided general consent were included in the ZOPAT cohort, with the baseline marked by the start of OPAT. To participate in ZOPATlife, patients needed to give written consent (only 47.2% did so) and undergo two interviews to assess any changes in quality of life. In this context, the baseline also refers to the beginning of OPAT, specifically at the time of the first questionnaire. Hence, the baseline is the same for both the first and second scenario.

To improve clarity we added a sentence in the section "study design and participants (line 104)

"*The baseline was established at the time of the first interview and start of OPAT.*"

5. Pg. 41, ll. 222-223: The sentence "The SF-36 scores for all domains were lower at baseline for inpatients than for outpatients 222 but never reached the levels observed in the Swiss

population." is confusing. Please consider splitting it into two sentences so that it doesn't read like low SF-36 scores are better.

Answer: We agree and revised the sentence. It now reads: "*The SF-36 scores for all domains were higher for outpatients compared to the baseline for inpatients. However, the SF-36 scores for both inpatients and outpatients did not reach the values observed in the Swiss population.*" (lines 189-191)

6. Pg 42, ll. 263-270: Some lines have been duplicated. Please delete.

Answer: We thank you for your attention. We have deleted the duplicate sentence (lines 228-229) "*This finding suggested that the combination of recovery from the disease and home-based treatment significantly impacts HRQoL.*"

7. Pg. 44, ll. 309: The sentence: "This study suggests that the better HRQoL scores achieved are likely due to outpatient treatment rather than general recovery from illness." is confusing. I don't think your study in itself suggests that better HRQoL scores are due to OPAT, but that is rather a point you wish to argue in the discussion, which you do well. Please consider revising that sentence.

Answer: Thank you for your feedback. We understand your concern regarding the phrasing. To clarify, our intention was not to imply that the study definitively demonstrates that improved HRQoL scores are solely due to OPAT. Rather, we meant to highlight that the data suggest a potential association between outpatient treatment and better HRQoL outcomes, though this finding should be interpreted cautiously, as other factors like general recovery may also play a role. We revised the wording to better reflect this nuance . (lines 265-266)

"The data suggest a potential association between outpatient treatment and better HRQoL outcomes, though this finding should be interpreted cautiously."

In general, I suggest you revise the order of the different sections in the discussion so that the sections about selection bias follow each other and the sections about the effect of OPAT vs. convalescence follow each other.

Answer: We are uncertain about the specific changes the reviewer recommends for the discussion. We propose moving a paragraph to enhance clarity and flow. (lines 256-259)

We also tried to minimize a possible selection bias by comparing the ZOPAT cohort to the ZOPATlife cohort. The groups showed no significant differences in demographic characteristics, but patients included in ZOPATlife more frequently received their therapy through an elastomeric pump. This likely stems from the fact that these therapies are often initiated for patients undergoing extended antimicrobial treatment, increasing their likelihood of enrolling in ZOPATlife.

8. Pg 46, l. 348: Please insert domains after HRQoL.

Done as suggested by the reviewer. The sentence now reads “Patients experienced significant improvements in HRQoL domains from just before discharge to the period in OPAT.” (line 291)

VERSION 3 - REVIEW

Reviewer 3
Name Borchmann, Olivia
Affiliation Copenhagen University Hospital, Infectious Diseases, Hvidovre Hospital
Date 04-Nov-2024
COI

The authors have adequately addressed all comments. I have no further comments.